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Childhood tumor risk after treatment with ovulation-stimulating drugs

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Objective: To assess childhood cancer risk among children conceived following the use of ovulation-stimulating drugs.

Design: Record linkage study.

Setting: Infertility patients and their offspring as identified through medical records.

Patient(s): Cohort of 30,364 Danish women evaluated for infertility beginning in the early 1960s.

Main Outcome Measure(s): Standardized incidence ratios (SIRs) compared cancer incidence in the children to the Danish population. Case-cohort techniques calculated rate ratios (RRs) according to prior maternal drug exposures.

Result(s): A total of 51 cancers were identified among the study children, resulting in an SIR of 1.14 (95% confidence interval [CI] 0.8–1.5). Usage of any fertility drug was associated with an RR of 0.82 (95% CI 0.4–1.6) and clomiphene citrate with an RR of 0.77 (95% CI 0.4–1.6). Tumors occurring early in life and nonhematopoietic malignancies (including neuroblastomas) were not associated with drug usage. Nonsignificant elevations in the risk of cancers occurring later in life, especially childhood hematopoietic malignancies (RR for use of any ovulation-stimulating drugs of 2.30, 95% CI 0.8–6.6), may have been related to underlying reasons for medication usage.

Conclusion(s): Although the findings of this study are reassuring, additional adequately powered studies should continue monitoring the effects of ovulation-stimulating drugs on specific tumors, including hematopoietic malignancies. (Fertil Steril® 2004;81:1083–91. ©2004 by American Society for Reproductive Medicine.)

Key Words: Childhood cancer, risk, infertility, clomiphene citrate

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The numbers of women who are delaying childbearing and using artificial means to stimulate ovulation have increased substantially over time. The consequences of such exposures on the outcomes of the pregnancies are unclear. Although increased risks of multiple births have been well documented (1), less is known about other health effects in children conceived following various treatments for infertility. Some attention has focused on the risk of malformations, including neural tube defects (2), but there has been little investigation regarding childhood cancer risk, despite a number of clinical reports linking either in vitro fertilization (IVF) or exposure to ovulation-stimulating drugs to neuroectodermal (3–5), hepatic (6, 7), or hematopoietic (3) malignancies. Only a limited number of follow-up studies have evaluated the issue of childhood cancer among children conceived following IVF therapy, and none had sufficient sample sizes or durations of follow-up to draw any definitive conclusions (8–12). Notably, each of these studies had data pertaining to only seven or fewer observed cases of childhood cancers.

Studies that have linked increases in the risk of certain childhood malignancies to preconceptional or in utero exposures to radiation or exogenous hormones (including diethylstilbestrol [DES]) provide further stimulus for evaluating risks among children conceived following efforts to stimulate ovulation (13). In addition, animal experiments have linked exposure of germ cells to carcinogens and mutagens to tumors in offspring (14). Thus, in an established cohort of women evaluated for in-

fertility in Denmark, we undertook an investigation to determine whether the children who were conceived as a result of the use of ovulation-stimulating drugs experienced any alteration in the risk of various childhood tumors.

MATERIALS AND METHODS

The study population was based on children delivered to a cohort of women whose admission to a hospital or private fertility clinic in Denmark, beginning in the early 1960s, resulted in a diagnosis of infertility. These patients were identified from medical files, microfilms, and local computerized systems. The Danish National Patient Register, which contains virtually all somatic discharges from hospitals since 1977, was also checked as a source for eligible patients. A total of 54,379 women were included in the infertility cohort. A Scientific Ethical Committee and a Data Protection Board in Denmark approved the study.

All available medical visits for these patients were reviewed; hospital records, which always included outpatient records, facilitated this review. Information was abstracted on surgical and medical interventions for infertility, including the types of infertility drugs prescribed and the number of treatment cycles. For each cycle, dates of starting and stopping were abstracted to define the windows of exposure to these drugs. Dosage information was also recorded, although, in many instances, this information was not available.

A Central Personal Register (CPR) was established in Denmark on April 1, 1968, when all citizens were assigned a unique 10-digit personal number. The computerized CPR includes information on migration and death on all inhabitants of the country, and is updated on a weekly basis. The CPR also includes ways to link parents and children if both were alive on (or after) April 1968, and the child was born after January 1953.

The infertility cohort was linked to this register for verification of CPR numbers and to obtain information on migrations and deaths of the women through the end of 1996.

Of the 54,379 women identified as eligible for study, all but 17 were found to have valid identification numbers in the CPR. An additional 2,894 women were excluded from the present analysis because they entered the cohort after December 31, 1996, leaving a total of 51,468 women for study.

The identification of the children born to women in this cohort is schematically depicted in Figure 1. To identify the children, we linked the cohort with the Medical Birth Register, which contains information on all births in Denmark since 1973, and with the CPR. A total of 54,275 births were registered in the period 1973–1996, which was covered by both registers. Of these, 384 stillbirths, 6,233 foreign adoptions, 965 Danish adoptions, and 137 births with uncertain nationality were excluded, leaving 46,556 children identified from the Medical Birth Register. We also linked the cohort to the CPR to obtain information on liveborn children during the time period not covered by the Medical Birth Register (1953–1972). During this period, 4,847 children were identified. From these, we excluded 336 foreign adoptions and 4 with unknown nationality. Thus, a total of 51,063 children (born to 30,364 women) were eligible for study.

To identify tumor cases among the children (0–20 years), the cohort was linked to the Danish Cancer Registry, which has recorded tumor incidence nationwide in Denmark since 1943.

Cohort Study

In the total cohort of 51,063 children, the mean follow-up time was 10.1 years, resulting in a total of 518,175 person-years of observation. A total of 16,786 children were born before the mother entered the cohort (258,187 person-years) and 34,277 were born during follow-up (259,988 person-years) of the mothers. The children were followed for cancer occurrence from the date of birth until date of emigration, date of death, or December 31, 1996, whichever came first. A total of 105 children were diagnosed with cancer: 54 born before and 51 cases born after the mother's entrance in the cohort. This cancer occurrence of children born after entry of the mothers into the infertility cohort was compared with that of the general population.

Case-Cohort Study

Cases

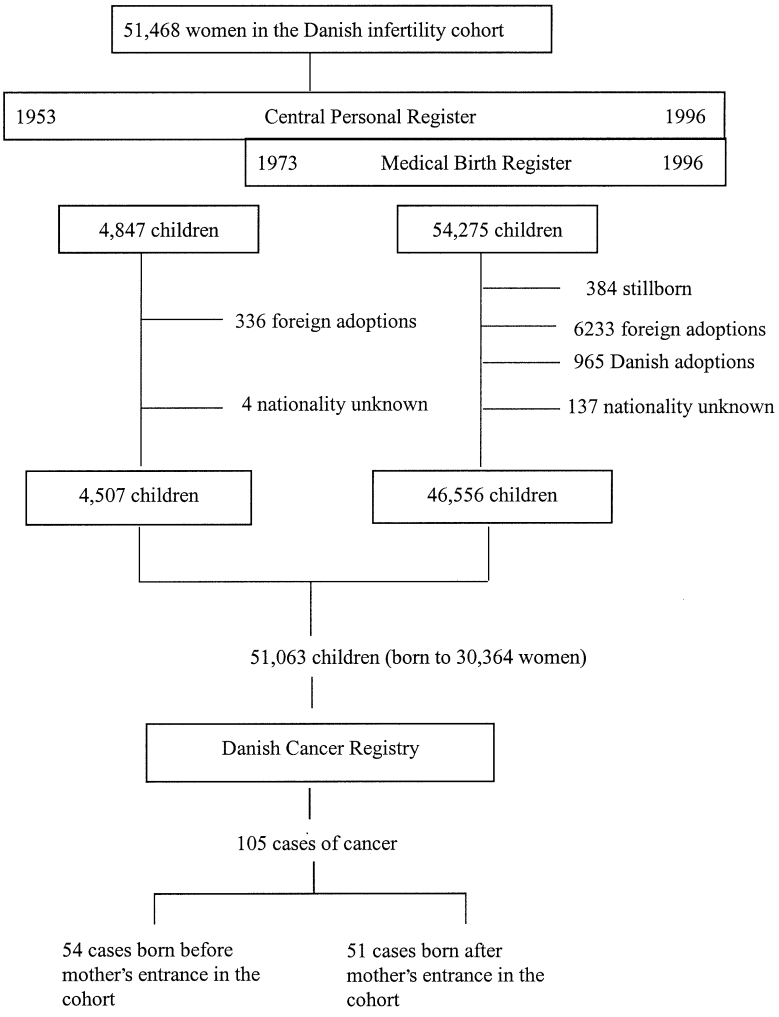
The mothers' hospital files related to infertility were requested from the respective hospitals/clinics for the 51 children who developed cancer subsequent to their mothers being evaluated for infertility. For 3 cases, the files could not be found and for 1 case the infertility diagnosis could not be confirmed, leaving 47 cases for analysis.

Subcohort

The study design in the analyses of the associations with specific infertility treatment was a case-cohort design, as described in Prentice (15), where the experience of all cases is compared to the experience of a randomly selected subcohort. In the present study, the subcohort included all children of a stratified random sample of 1,360 women who were originally selected as a comparison subcohort in a case-cohort analysis of cancer risk in the mothers. The stratification used in the original sampling of the mothers was based on age and calendar year of entry to the infertility cohort. Among these women, 868 gave birth, resulting in 1,507 children. We excluded 323 children born before 1973 and 217 children born before the mother entered the infertility cohort, leaving 967 children. The hospital files regarding infertility could not be obtained for 42 mothers giving birth to 57 children. For 3 mothers with 3 children, the infertility diagnosis could not be confirmed in the hospital files, and for an additional 10 mothers with 13 children, the infertility was caused by a previous sterilization. These children were excluded, leaving 894 children in the subcohort, of whom 3 were also cases.

FIGURE 1

Identification of the children born to women in the Danish infertility cohort.



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Because the children in the subcohort only provide information in strata where cases are observed, only 868 subcohort children (including 3 cases) contributed to the analysis. For the same reason, a lower, varying number of subcohort children contributed to each of the case-subset analyses performed. In the subset analyses of cancer cases after 5 years of age, the number of subcohort children contributing was further diminished because 158 subcohort children were censored before the age of 5 years.

Statistical Methods

Cohort Analyses

To assess the risk of tumors among children born to mothers after entry into the infertility cohort, expected numbers of tumors were derived by multiplying the person-years of observations in each 5-year age group by age, sex, and calendar-specific incidence rates for tumor occurrence. Expected rates were available for the time period 1943–1996 from the Danish Cancer Registry. This enabled the calculation of standardized incidence ratios (SIRs), defined as the ratio of the observed numbers of tumors to those expected. Ninety-five percent confidence intervals (CI) were calculated on these SIRs based on the assumption that the observed numbers followed a Poisson distribution.

Case-Cohort Analyses

The statistical analyses of the associations with specific infertility treatments were based on Cox's proportional hazards regression model using age of the child as time scale and stratifying according to the sampling strata used in the

TABLE 1

Standardized incidence ratios of childhood tumors among children born subsequent to their mothers' evaluation for infertility (Danish cohort of patients with infertility, 1960–1996).

	After evaluation			
Type of tumor	Obs	Exp	RR	95% CI
All malignant neoplasms	51	44.7	1.14	0.8–1.5
Leukemias	18	13.9	1.29	0.8–2.0
Lymphomas	4	3.6	1.10	0.3–2.8
CNS and related tumors	12	12.0	1.00	0.5–1.7
Sympathetic nervous system tumors	7	3.3	2.14	0.9–4.4
Retinoblastomas	1	1.6	0.63	0.0–3.5
Renal tumors	3	2.7	1.10	0.2–3.2
Hepatic tumors	1	0.5	1.86	0.0–10.4
Malignant bone tumors	1	1.3	0.78	0.0–4.4
Soft-tissue sarcomas	2	2.5	0.81	0.1–2.9
Germ cell, trophoblastic, and other gonadal tumors	0	1.5	0	
Carcinoma and other malignant epithelial neoplasms	2	1.4	1.42	0.2–5.1

Note: RR = rate ratio; CI = confidence interval; CNS = central nervous system.

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selection of the subcohort. The estimation of the rate ratios was performed as suggested in Prentice (15), where all subcohort children contribute to all relevant risk sets until end of follow-up due to cancer diagnosis, death, or censoring, whereas case children outside the subcohort only enter their own risk set. The confidence limits and tests were based on robust estimates of the variance–covariance matrix of the Cox regression parameters.

Because a single child was randomly selected from each study mother, and the number of eligible children per family varied from family to family, we also conducted regression analyses where the observations for the study children were weighted by the inverse of the sampling fraction — namely, the number of eligible children in the family. Results from these analyses were nearly identical to those that did not account for the sampling fraction; therefore, only the nonweighted results are presented.

RESULTS

A total of 51 children born subsequent to their mothers having been evaluated for infertility were found to have developed cancer. Their cancer risk was found to be comparable to that of the general population of children in Denmark (Table 1), with an SIR of 1.14 (95% CI 0.8–1.5). The SIR for leukemias was 1.29 (0.8–2.0), while that for lymphomas was 1.10 (0.3–2.8). The SIR was nonsignificantly elevated for sympathetic nervous system tumors (SIR = 2.14, 0.9–4.4), but this was based on only seven observed cases.

Subsequent analyses used a case-cohort approach to explore potential relationships with exposure to maternal use of ovulation-stimulating drugs before the birth of the child of interest, focusing on cancer in children born after entry of the mothers into the infertility cohort (Table 2). Although the risks were similar for male and female children, there was some evidence that children whose mothers were 30 years of age or older at their birth were at somewhat higher risk than children of younger mothers. However, the trend in risk with maternal age was not statistically significant (P=.26). After adjustment for maternal age, there was no relationship to the risk of ever having used ovulation-stimulating drugs before the birth of the child (RR = 0.82, 95% CI 0.4–1.6) or with cycles of stimulation. In addition, there was no relationship of risk with any of the treatment parameters considered, including the prior use of clomiphene citrate (clomiphene) (RR = 0.77), human chorionic gonadotropin (hCG) (0.69), or human menopausal gonadotropin (hMG) (0.59). Furthermore, risk was not influenced by the number of cycles of clomiphene received. Numbers of women receiving other treatment modalities or combined modalities were too limited for detailed investigations.

Additional analyses considered relationships by age of the child at development of their tumor and by types of tumors that developed. The majority of tumors were diagnosed when the children were less than 5 years of age (Table 3), but among these children, no evidence was found of any association of risk according to the prior use of ovulation-stimulating drugs or use of specific treatment parameters. In addition, age of the mother at the time of birth was not a predictor of risk of these early onset cancers. In contrast, among the children whose tumors were diagnosed between the ages of 5 and 20 years of age, some evidence of increasing risk was found with advancing maternal age at their birth. However, neither the trend of risk with increasing

TABLE 2

Rate ratios of childhood tumors by birth characteristics and maternal exposure to ovulation-stimulating drugs before the birth of the child.

	No. of cases	No. in subcohort	RR	95% CI
Sex of the child				
Male	24	439	1.00	—
Female	23	429[a]	1.10	0.6–2.0
Age (y) of mother at birth of study subject				
<30	15	256	1.00	—
30–32	14	210[a]	1.57	0.7–3.3
33–35	12	220[b]	2.40	1.0–5.6
≥36	6	182	1.71	0.5–5.5
			Trend P=.26	
Ever ovulation-stimulation[d]				
No	30	524[b]	1.00	—
Yes	15	334[a]	0.82	0.4–1.6
Unknown	2	10	—	—
Cycles of ovulation-stimulation[d]				
Never	30	524[b]	1.00	—
1–2	7	92	1.50	0.6–3.7
≥3	6	228[a]	0.48	0.2–1.2
Unknown	4	24	—	—
Ever clomiphene[d]				
No	34	594[b]	1.00	—
Yes	11	265[a]	0.77	0.4–1.6
Unknown	2	9	—	—
Cycles of clomiphene[d]				
Never	34	594[b]	1.00	—
1–2	5	82	1.20	0.4–3.4
≥3	5	180[a]	0.51	0.2–1.5
Unknown	3	12	—	—
Ever hCG[d]				
No	35	600[b]	1.00	—
Yes	10	260[a]	0.69	0.3–1.5
Unknown	2	8	—	—
Ever hMG[d]				
No	44	779[c]	1.00	—
Yes	2	83	0.59	0.1–3.1
Unknown	1	6	—	—

Note: RR = rate ratio; CI = confidence interval; hCG = human chorionic gonadotropin; hMG = human menopausal gonadotropin.

[a] Includes one case.

[b] Includes two cases.

[c] Includes three cases.

[d] Adjusted for mother's age at birth of study subject.

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maternal age nor the risk associated with a birth after age 30 was statistically significant. After adjusting for maternal age, there was a nonsignificant elevation in risk associated with ever use of ovulation-stimulating drugs (RR = 1.51, 95% CI 0.6–4.1). This primarily reflected a high risk associated with prior use of hMG. Although the associated risk was statistically significant, it was based on only two exposed cases (RR = 6.24, 95% CI 1.1–36.0).

To assess whether the effect of drug exposure varied by tumor type, tumors were subdivided into three groups: hematopoietic malignancies (n = 19), neural tumors (n = 19), and other tumors (n = 9) (Table 4). Previous use of ovulation-stimulating drugs, or specifically of clomiphene, was not associated with an increase in the risk of neural or the other tumors, even when specific attention was given to the subclassification of tumors known as "sympathetic nervous system tumors," the classification of tumors showing some elevation in risk in the cohort analyses. In fact, prior use of any ovulation-stimulating drug was associated with a significant decrease in the risk of all neural tumors (RR = 0.26, 95% CI 0.1–0.9), based on 3 exposed cases. Although age of the mother at birth of the study subject was not related to

TABLE 3

Rate ratios of childhood tumors by age at diagnosis according to birth characteristics and maternal exposure to ovulation-stimulating drugs before the birth of the child.

	Cancer in children 0–4 years of age				Cancer in children 5–20 years of age			
	No. of cases	No. in subcohort	RR	95% CI	No. of cases	No. in subcohort	RR	95% CI
Sex of the child								
Male	14	393[b]	1.00	—	8	232	1.00	—
Female	16	380[a]	1.42	0.7–3.1	6	226	0.77	0.3−2.0
Age (y) of mother at birth of study subject								
<30	11	195	1.00	—	4	203	1.00	—
30–32	9	195[a]	1.24	0.5–2.9	4	131	2.00	0.5−8.1
33–35	7	211[b]	1.40	0.5–4.0	3	71	3.42	0.8−14.8
≥36	3	172	0.63	0.2–2.3	3	53	5.86	0.9−38.8
			Trend P=.71				Trend P=.24	
Ever ovulation-stimulation[d]								
No	20	462[b]	1.00	—	8	302	1.00	—
Yes	8	301[a]	0.53	0.2–1.3	6	151	1.51	0.6−4.1
Unknown	2	10	—	—	0	5	—	—
Ever clomiphene[d]								
No	22	526[b]	1.00	—	10	343	1.00	—
Yes	6	238[a]	0.50	0.2–1.3	4	110	1.22	0.4−3.3
Unknown	2	9	—	—	0	5	—	—
Ever hCG[d]								
No	22	529[b]	1.00	—	11	336	1.00	—
Yes	6	236[a]	0.56	0.2–1.5	3	117	0.82	0.2−3.2
Unknown	2	8	—	—	0	6	—	—
Ever hMG[d]								
No	29	689[c]	1.00	—	12	434	1.00	—
Yes	0	78	—	—	2	19	6.24	1.1−36.0
Unknown	1	6	—	—	0	5	—	—

Note: RR = rate ratio; CI = confidence interval; hCG = human chorionic gonadotropin; hMG = human menopausal gonadotropin.

[a] Includes one case.

[b] Includes two cases.

[c] Includes three cases.

[d] Adjusted for mother's age at birth of study subject.

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either the neural or other tumors, some evidence of a trend in risk existed with this variable for the hematopoietic tumors; the test for trend, however, was not statistically significant. After adjustment for maternal age, there was a nonsignificant elevation in the risk of hematopoietic malignancies associated with use of ovulation-stimulating drugs (RR = 2.30, 95% CI 0.8−6.6). Risk was also nonsignificantly elevated for use of clomiphene (1.78, 0.6−4.8) and hCG (1.54, 0.5–4.7). All these risks were based on relatively small numbers of exposed cases (10, 7, and 7, respectively). The majority of the hematopoietic tumors were leukemias (15 of the 19), specifically lymphatic leukemias (12 cases). Analyses restricted to only the leukemias resulted in risk estimates similar to those observed for all hematopoietic malignancies.

DISCUSSION

The issue of whether treatments to stimulate ovulation have an effect on the offspring of subsequent pregnancies is an important question, especially given increasing numbers of women who are availing themselves of such pregnancy assistance. Despite this, there has been only limited attention regarding health effects, with few studies focusing specifically on carcinogenic effects. The results from our study were largely reassuring and suggested that no overall increase in tumor risk occurred among children conceived following their mothers' treatments for infertility. However, even though this is the largest study to date, we were limited in our ability to detect alterations in risk, especially for specific tumor types.

In terms of overall cancer risk, the results from our study were consistent with the previous population-based studies that have been conducted, all of which have had extremely limited sample sizes for evaluating cancer risks. All of these previous studies have been based on cohorts of women receiving IVF, and thus differed from our approach, which

TABLE 4

Rate ratios of specific types of childhood tumors by birth characteristics and exposure to ovulation-stimulating drugs before the birth of the child.

	Hematopoietic[e]				Neural[f]				Others[g]			
	No. of cases	No. in subcohort	RR	95% CI	No. of cases	No. in subcohort	RR	95% CI	No. of cases	No. in subcohort	RR	95% CI
Sex of the child												
Male	9	307[a]	1.00	—	12	362[a]	1.00	—	3	224	1.00	—
Female	10	317	1.07	0.4–2.7	7	334[b]	0.72	0.3–1.9	6	214	3.02	0.6–14.7
Age (y) of the mother at birth of study subject												
<30	5	243	1.00	—	6	186	1.00	—	4	154	1.00	—
30–32	7	171[a]	2.75	0.8–9.3	3	179	0.66	0.2–2.6	4	131	1.99	0.5–7.3
33–35	4	128	3.27	0.8–13.7	7	178[b]	2.33	0.6–8.8	1	82	0.89	0.2–4.8
≥36	3	82	4.42	0.8–25.7	3	153	1.02	0.2–5.1	0	71		
		Trend P=.28				Trend P=.38				Trend P=.46		
Ever ovulation-stimulation[d]												
No	9	390	1.00	—	15	407[b]	1.00	—	6	271	1.00	—
Yes	10	227[a]	2.30	0.8–6.6	3	281	0.26	0.1–0.9	2	161	0.67	0.1–3.3
Unknown	0	7	—	—	1	8	—	—	1	6	—	—
Ever clomiphene[d]												
No	12	443	1.00	—	15	466[b]	1.00	—	7	309	1.00	—
Yes	7	174[a]	1.78	0.6–4.8	3	223	0.37	0.1–1.4	1	123	0.34	0.1–2.4
Unknown	0	5	—	—	1	8	—	—	1	6	—	—
Ever hCG[d]												
No	12	442	1.00	—	16	468[b]	1.00	—	7	301	1.00	—
Yes	7	177[a]	1.54	0.5–4.7	2	220	0.24	0.1–1.1	1	131	0.44	0.0–4.4
Unknown	0	5	—	—	1	8	—	—	—	—	—	—
Ever hMG[d]												
No	18	571	—	—	17	619[b]	1.00	—	9	400	1.00	—
Yes	1	48[a]	—	—	1	71	—	—	0	32	—	—
Unknown	0	5	—	—	1	6	—	—	0	6	—	—

Note: RR = rate ratio; CI = confidence interval; hCG = human chorionic gonadotropin; hMG = human menopausal gonadotropin.

[a] Includes one case.

[b] Includes two cases.

[c] Includes three cases.

[d] Adjusted for mother's age at birth of study subject.

[e] Includes 12 lymphatic leukemias, 3 myeloid leukemias, 2 Hodgkin's disease, and 2 lymphomas.

[f] Includes 6 neuroblastomas, 3 medulloblastomas, 2 astrocytomas, 1 neuroepithelioma, 1 craniopharyngioma, 1 ependymomablastoma, 1 embryonal rhabdomyosarcoma, and four brain, not otherwise specified.

[g] Includes 3 Wilms' tumors, 1 testicular tumor, 1 thyroid carcinoma, 1 retinoblastoma, 1 chordoma, 1 heptoblastoma, and 1 melanoma.

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focused on a wider group of women receiving ovulation-stimulating agents.

The largest previous study, a population-based historical cohort in The Netherlands, compared cancer rates for 9,484 children conceived after IVF with 7,532 children conceived naturally among mothers with subfertility disorders and observed 7 cancers vs. 7.1 expected (8). In the next largest study, a follow-up of obstetric outcomes of 5,856 infants conceived after IVF in Sweden, only 4 cancers were detected, a number not in excess of the 3.6 cancers expected (9). Similarly, in an Australian follow-up study of 5,249 births occurring after IVF, 6 cancers were observed vs. 4.3 expected (10). In a United Kingdom study involving 2,507 births after IVF, 2 cancers were observed vs. 3.5 expected (11). Finally, in a small study in Israel, which followed 332 children born after IVF, no cancer cases were observed vs. 1.7 expected (12).

Several clinical studies suggest that the impact of ovulation-stimulating drugs on the health of the offspring may be specific for certain tumor types. White et al. (5) reported three cases of neuroectodermal tumors (two neuroblastomas and one medulloblastoma) in children born after IVF and two tumors (one neuroblastoma and one supratentorial primitive neuroectodermal tumor) in children conceived after ovulation induction with clomiphene and artificial insemination. Toren et al. (7) described two children who developed

hepatoblastoma and clear cell sarcoma of the kidney after IVF pregnancies. An additional report described the possible association between maternal use of gonadotropins and the development of hepatoblastoma in the offspring (6). Further, Kobayashi et al. (3) reviewed the mother's drug history before pregnancy in 6,236 cases of childhood malignancies diagnosed between 1985 and 1989, finding 9 childhood cancer cases (4 neuroblastomas, 3 malignant lymphomas, and 2 reticuloendothelial tumors) in children born to mothers who underwent ovulation stimulation. Thus, from these collective reports, there emerges some concern regarding a possible effect on neuroectodermal malignancies, including neuroblastomas.

Several case-control studies also raise concern about a potential impact of preconceptional or in utero exposures on the risk of neuroblastomas (4, 16–18). The largest risk was noted in a study by Michalek et al. (17), which found a threefold increase in risk for any usage of sex hormones during pregnancy, and over a tenfold increase if usage was specifically for infertility. However, this estimate was based on exposure in only five cases and one control.

In a study by Kramer et al. (16), sex hormone exposure 3 months before or during pregnancy resulted in an odds ratio of 2.25, although only 2 case mothers and 1 control mother specifically reported drug use for infertility problems.

Olshan et al. (18), in the largest study to date, found no association with use of oral contraceptives before or during pregnancy, but a 1.6-fold increased risk associated with clomiphene use. However, this association derived from exposures that occurred long before the index pregnancy (and not periconceptionally or during the index pregnancy), raising questions as to the biologic plausibility of the association. Further, in a study by Schwartzbaum et al. (19), no relationship of risk of neuroblastoma was observed following in utero exposure to sex hormones.

In our study, we did not find any evidence from either the cohort or the case-cohort analyses of an increase in the risk of neuroblastomas among children conceived following use of ovulation-stimulating drugs. In our cohort analyses, we did find a modest increase in the risk of sympathetic nervous system tumors among the subjects born after their mothers had entered the infertility cohort, although based on only seven cases. However, our case-cohort analyses failed to identify any specific infertility treatment that would account for this elevation.

Several previous investigations have also suggested that hormone use related to infertility might be associated weakly with childhood leukemias (20–21). Another investigation suggested that any elevations in the risk of childhood cancers might relate more to the causes of infertility than to specific drug exposures (22). Our case-cohort analyses suggested a possible increased risk of hematopoietic malignancies (primarily leukemias) associated with use of both clomiphene and hCG. However, both risks were based on small numbers and did not achieve statistical significance.

We also found some evidence that the risk of these malignancies might be associated with age of the mother at the birth of the study subject, although again the relationship was not statistically significant. Although we attempted to adjust effects of usage of ovulation-stimulating drugs for maternal age effects, the small numbers of exposed cases hindered our ability to achieve complete control. In addition, we were not able to account for causes of infertility that might have led to delays in ages at first birth. Thus, given the small numbers involved, as well as the lack of information on the indications for drug usage, it is difficult to discern the underlying reasons for the slight excess risk of leukemia among mothers who had used ovulation-stimulating drugs. The fact that the association with maternal age was considerably stronger than that associated with use of ovulation-stimulating drugs suggests that intrinsic maternal factors may have been a more important contributor to our observed elevation in risk, as has been suggested previously (22).

Although our study was considerably larger than the previous investigations that have addressed the issue, we nevertheless had limited power to evaluate the effects of ovulation-stimulating drugs, particularly as related to specific tumor types. Given the likely etiologic diversity of childhood tumors, this was a major limitation of our study. Thus, our sample size provided 80% power to detect approximately a threefold excess risk for all tumors, but considerably lower power to detect tumors of most interest — namely, the neuroectodermal and hematopoietic malignancies, which have been linked in some clinical series and epidemiologic investigations with exposure to ovulation-stimulating drugs. In addition, given our limited follow-up, we had very limited power to assess risk for tumors that occur at older ages, such as Hodgkin's lymphoma and bone and testicular cancers — malignancies that typically occur during adolescence and beyond.

Several other methodologic limitations of this investigation bear mention. Although, in most cases, we were able to determine whether use of ovulation-stimulating drugs preceded conception, we did not have precise information on when conception occurred; thus, information on the timing of drug usage with respect to conception was not analyzed. Given the known fact that clomiphene is excreted slowly and may still be present 6 weeks after its administration (23), and that it produces elevated levels of E_2 and P in the early stages of pregnancy, both preconceptional as well as in utero influences must be considered.

Difficulties in appropriately defining windows of exposure are well recognized in this area of research (13). Although few examples of preconceptional exposures that lead to carcinogenic effects are available, a number of examples of in utero exposures are available. Clomiphene exposure close to or following the time of conception has also been

linked with various fetal growth and development alterations (24–25). Thus, continued surveillance of carcinogenic effects appears warranted.

Despite the limitations of our investigation, it did provide substantially more information than previous studies on the issue. We also had the benefit of having exposure data that was not dependent on patient recall. Although our findings are reassuring in not showing any elevation in the risk of childhood cancers associated with various infertility treatments, it is clear that these exposures are in need of continued evaluation, particularly in populations that can expand on our limited findings. In particular, further scrutiny is needed regarding effects on specific tumor types. These include childhood hematopoietic malignancies that were nonsignificantly elevated among users of ovulation-stimulating drugs in our study and neuroectodermal tumors, which have been linked to ovulation-stimulating drugs in previous investigations. A more comprehensive evaluation of these exposures will be dependent on the unbiased assessment of exposure data, including information that is detailed with respect to the timing of conception and delivery.

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